REMARKS

Upon entry of the foregoing amendment, claims 1-34 are pending.

The amendments to the specification are for editorial purposes. No new matter has been added to the specification.

The amendment to claim 30 is to replace the phrase "acetylcholine esterase" with the more acceptable term in the art, namely "acetylcholinesterase".

No new matter has been added to the claims.

Please find attached a marked up version of the specification and of said claim entitled "Version with Markings to Show Changes Made".

Respectfully submitted,

Yuji ISHIHARA et al.

By _____
Warren M. Cheek, Jr.
Registration No. 33,367
Attorney for Applicants

JJF/WMC/jlw
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
October 12, 2001

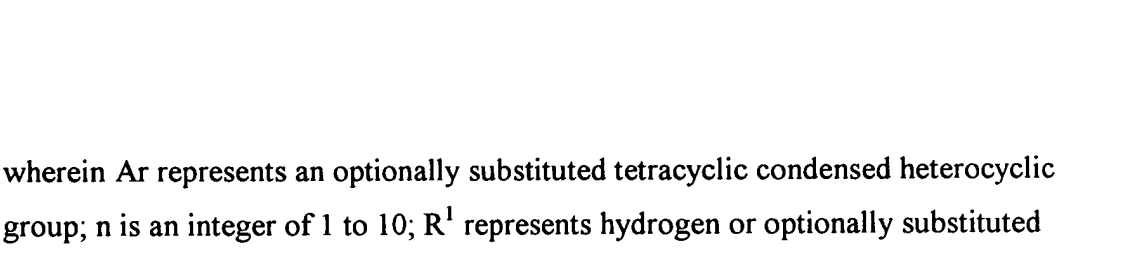
Version with Markings to Show Changes Made

30. (Amended) An [acetylcholine esterase] acetylcholinesterase inhibitor comprising the pharmaceutical composition according to claim 29.

ij]quinolin-4-one, 1-(1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone, and the like.

Also described in the Japanese Patent Kokai Publication is an amorphous substance of 8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof, which possesses an action to inhibit acetylcholine esterase.

(6) Compounds of the following formula:



wherein Ar represents an optionally substituted tetracyclic condensed heterocyclic group; n is an integer of 1 to 10; R^1 represents hydrogen or optionally substituted hydrocarbon group, which may be different according to a repetition of n; Y represents an amino or nitrogen-containing saturated heterocyclic group, each of which may have a substituent or substituents; or salts thereof as described in JP-A 7-309835/1995.

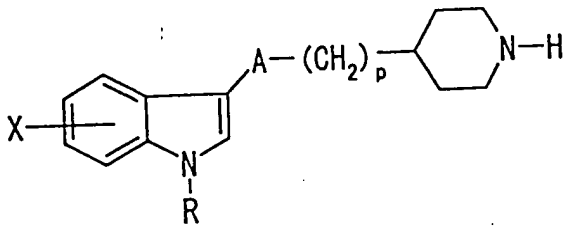
Such compounds as described above are exemplified by 3-[3-[1-(phenylmethyl)-4-piperidinyl]-1-oxopropyl]-7,11b,12,13-tetrahydro-5H-isoindolo[2,1-b][2]benzazepin-7-one, 2-[1-oxo-3-[1-(phenylmethyl)-4-piperidinyl]-4,5,7a,8,9,10,11,11a-octahydro-6H-pyrido[3,2,1-jk]carbazol-6-one, and the like.

(7) Amine compounds described in WO 93/07140, PCT Japanese Patent Unexamined Publication No. (hereinafter referred to as PCT JP-A) 6-500794/1994, JP-A 4-234845/1992, JP-A 6-116237/1994, JP-A 7-109275/1995, WO 97/37992, JP-A 5-148228/1993, JP-A 5-194359/1993, JP-A 6-507387/1994, PCT JP-A 7-502272/1995, PCT JP-A 8-511515/1996, JP-A 6-41070/1994, JP-A 5-9188/1993, JP-A 5-279355/1993, JP-A 5-320160/1993, JP-A 6-41125/1994, JP-A 5-345772/1993, JP-A 7-502529/1995, JP-A 64-79151/1989, JP-A 62-234065/1987, JP-A 4-235161/1992, JP-A 4-21670/1992, JP-A 9-268176/1997, and so on.

(8) Amine compounds described in JP-A 2-167267/1990, JP-A 63-166881/1988, JP-A 2-96580/1990, JP-A 3-153667/1991, JP-A 61-148154/1986,

C_{1-3} alkoxy, halogen or C_{1-3} alkylthio; R^9, R^{10}, R^{11}, R^{12} and R^{13} each represent hydrogen, C_{1-5} alkyl or phenyl, R^{10} and R^{11} together may form a C_{3-6} alkylene chain, R^{12} and R^{13} together may form a C_{3-6} alkylene chain; a or b indicates a double bond or single bond, but they are not double bonded at the same time;
or pharmacologically acceptable salts thereof which can be used as antipsychotics.

(2) JP-A 52-72829/1977 describes compounds of the following formula:

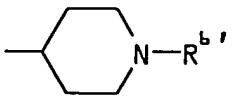


wherein R is hydrogen, alkyl containing 1 to 4 carbon atoms, or aralkyl of which the alkyl portion contains 1 or 2 carbon atoms; X is hydrogen or halogen, alkyl, alkoxy or alkylthio, each of which may contain 1 to 4 carbon atoms, trifluoromethyl, nitro, hydroxy or unsubstituted amino, or amino substituted by 1 or 2 alkyl groups or acyl or alkylsulfonyl; A is a group -CO- or $-CH_2-$; and n is 0, 1 or 2;
or salts thereof which can be used in treatment of diseases caused particularly by serotonergic dysfunction.

In these compounds, however, there is neither report, suggestion nor disclosure on their effect as prophylactics or therapeutic agents for dysuria (difficulty of urination) or on their effect as excretion improving agents for urinary bladder.

Therefore, it has been a desire to develop prophylactics or therapeutic agents for dysuria, particularly difficulty in urination, which have a high efficiency for urination and high versatility compared with known compounds known to have an effect in improving excretion of the urinary bladder.

There has also been a desire in the pharmaceutical industry to attain crystals that are good in absorbability and are used for an acetylcholine esterase inhibitor, an agent for improving the excretory potency of a urinary bladder, and a therapeutic agent against micturition disorders/dysuria disorders which are stable.



wherein $R^{6'}$ is benzyl which may be substituted by 1 or 2 substituents selected from halogen, C_{1-3} alkyl, C_{1-3} alkoxy, cyano, nitro and hydroxy;

(9) An agent as described in the above item (1) comprising 8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one,

8-[3-[1-(phenylmethyl)-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one,

8-[3-[1-[(2-hydroxyphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one,

or a salt thereof,

(10) An agent as described in the above item (1) which is a prophylactic and therapeutic agent for dysuria;

(11) An agent as described in the above item (1) which is a prophylactic and therapeutic agent for difficulty in urination;

(12) Agent for improving excretory potency of the urinary bladder which comprises a combination of an α-blocker and an amine compound of non-carbamate-type having an acetylcholinesterase-inhibiting action; and

(13) Crystals of a tricyclic, condensed, heterocyclic derivative and pharmaceutical compositions comprising the crystals, which possess an action to inhibit acetylcholinesterase and an action to improve the excretory potency of urinary bladder.

As a result of intensive investigations, the present inventors have succeeded in obtaining crystals of 8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one, which are high in purity, high in quality, low in hygroscopic property, and extremely excellent in stability without deteriorating upon long-term storage under usual conditions, thereby providing the second aspect of the present invention.

In other words, the present invention also relates to

(i) crystals of 8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,

(ii) the crystals described in the above-mentioned item (i), wherein the melting point is above 110°C,

(iii) the crystals described in the above-mentioned item (i), wherein the melting point is about 113°C to about 118°C,

(iv) a pharmaceutical composition which comprises the crystals described in the above-mentioned item (i),

(v) the pharmaceutical composition described in the above-mentioned item (iv), which is an acetylcholine esterase inhibitor,

(vi) the pharmaceutical composition described in the above-mentioned item (iv), which is an agent for improving the excretory potency of urinary bladder,

(vii) the pharmaceutical composition described in the above-mentioned item (iv), which is a therapeutic agent against micturition disorders,

(viii) the pharmaceutical composition described in the above-mentioned item (iv), which is a therapeutic agent against dysuria disorders, and

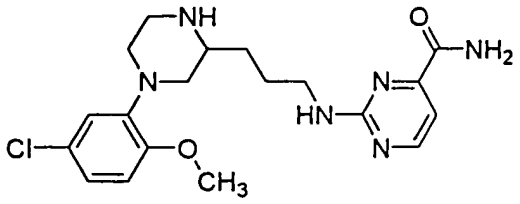
(ix) agents for improving the excretory potency of urinary bladder, which are characterized by combining crystals of 8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof with an α-blocker.

Brief Description of the Drawing

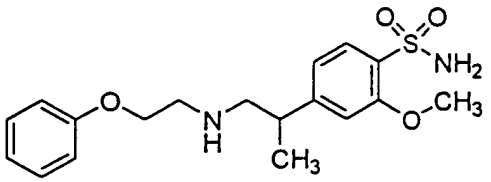
Figure 1 shows a powder X-ray crystal diffractometry pattern of the crystals obtained in Example 1.

Detailed Description of Preferred Embodiments

The "amine compounds of non-carbamate-type having an acetylcholinesterase-inhibiting action" used in the invention include those which have an acetylcholinesterase-inhibiting action but have no carbamate structure –OCON- in the molecule, and in which the hydrogen atom on ammonia is replaced by a hydrocarbon group, preferably including primary amine compounds, secondary amine



LY-23352



In addition, such α-blockers as ABT-980, AIO-8507-L, L-783308, L-780945, SL-910893, GI-231818, SK&F-106686, etc. are also included.

The crystals of the present invention have an activity to inhibit acetylcholinesterase. Therefore, the crystals of the present invention and the pharmaceutical compositions of the present invention can be used as the prophylactic and/or therapeutic agents against the senile dementia.

Also, the crystals of the present invention and the pharmaceutical compositions of the present invention can be used, for example, as agents for improving the excretory potency of urinary bladder. For instance, they can be used as the prophylactic and/or therapeutic agents against micturition disorders arising from the following 1) to 6) and the like, dysuria in particular: 1) prostatic hypertrophy, 2) bladder neck obstruction, 3) neurogenic bladder, 4) diabetes mellitus, 5) surgery, 6) hypotonic bladder, and 7) Sjoegren's syndrome (dry eye, dry mouth, dryness of vagina, and the like).

More specifically, they can be used as the prophylactic and/or therapeutic agents against dysuria that are caused by hypotonic bladder induced by prostatic hypertrophy, hypotonic bladder induced by diabetes mellitus, hypotonic bladder induced by diabetic neuropathy, idiopathic hypotonic bladder (including age-associated hypotonic bladder), hypotonic bladder induced by multiple sclerosis, hypotonic bladder induced by Parkinson's disease, hypotonic bladder induced by spinal

cord injury, postoperative hypotonic bladder, hypotonic bladder induced by brain block, neurogenic bladder induced by diabetes mellitus, neurogenic bladder induced by diabetic neuropathy, neurogenic bladder induced by multiple sclerosis, neurogenic bladder induced by Parkinson's disease, neurogenic bladder induced by spinal cord injury, neurogenic bladder induced by brain block, and the like.

Furthermore, the crystals of the present invention and the pharmaceutical compositions of the present invention can also be used as the prophylactic and/or therapeutic agents against micturition disorders such as pollakisuria, urinary incontinence, and the like.

Utilization in combination with another agent

The crystals of the present invention are those of a kind of non-carbamate amine compound possessing the action to inhibit acetylcholinesterase. A non-carbamate amine compound including that for the crystals of the present invention, which possesses the action to inhibit acetylcholinesterase, can be used in combination with a drug to treat diseases inducing micturition disorders (for example, dysuria and the like) or with a drug that is administered to treat other diseases but as itself induces micturition disorders (for example, dysuria and the like).

Such a "non-carbamate amine compound possessing the action to inhibit acetylcholinesterase" may be any compound possessing the action to inhibit acetylcholinesterase and not having the carbamate structure (-OCON-) within the molecule, wherein the hydrogen atom of ammonia is substituted with a hydrocarbon group, preferably being the primary amine compound, the secondary amine compound, or the tertiary amine compound. More preferably, there are set forth compounds 1) to 49) and the like that are described in the following. Among these compounds, compounds, which have at least one 5- to 7-membered, nitrogen-containing heterocyclic ring as a partial structure, and the like are preferable; compounds 1), 20), 23), 41), and 43), which are described hereinafter, and the like are especially preferable; and compound 1) and the like are particularly preferable.

Hereupon, because a variety of non-carbamate amine compounds described above possess the action to inhibit the acetylcholinesterase, they possess also an insecticidal action.

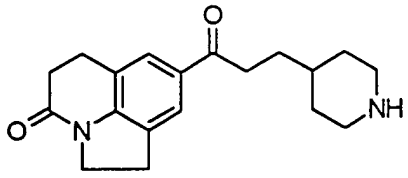
From the result of the above-mentioned Experimental Examples 2, 3 and 4, it is found that non-carbamate-type amine compounds showing an acetylcholinesterase-inhibiting action, particularly, Compounds (I) have a potent effect for improving excretory potency of the urinary bladder.

Examples Involving Crystals

The following Examples are drawn to the embodiments of the present invention involving crystals. The melting points were measured by using a Type-535 melting point apparatus produced by Büchi Company and a MP-500D apparatus manufactured by Yanako Kiki Kaihatsu Kenkyusyo Kabushiki Kaisya. The data on the powder X-ray crystal diffractometry are determined by using Type-RINT1100 (Rigaku Denki Kabushiki Kaisya) using the Cu-Kα_1 radiation as the radiation source. Also, in the following Reference Examples and Examples, % indicates the percent by weight, unless otherwise specified.

Reference Example 31

8-[3-(4-Piperidinyl)-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one



1) Into thionyl chloride (300 ml) was added 3-(1-acetyl-4-piperidinyl)propionic acid (88.2 g, 0.443 mol) in small portions under ice cooling. After the resulting mixture was stirred at room temperature for 10 minutes, the thionyl chloride was evaporated under reduced pressure at 25°C. The resulting residue was mixed with diethyl ether and was evaporated under reduced pressure to leave a yellow solid residue. An additional diethyl ether was added to the residue and the solid substance was subjected to pulverization by the use of a spatula, followed by evaporation under reduced pressure to obtain a crude product of 3-(1-acetyl-4-piperidinyl)propionyl chloride as a yellow powder. To a suspension of this yellow

^{1}HNMR ($CDCl_3$) δ 1.20-1.50 (4H, m), 1.55-1.80 (4H, m), 1.85-2.05 (2H, m), 2.71 (2H, t, J = 7.6 Hz), 2.80-3.15 (5H, m), 3.22 (2H, t, J = 8.6 Hz), 3.47 (2H, s), 4.13 (2H, t, J = 8.6 Hz), 6.85-7.15 (3H, m), 7.20-7.35 (1H, m), 7.67 (1H, s), 7.72 (1H, s).

Elemental analysis for $C_{26}H_{29}N_2O_2$,

Calcd.: C, 74.26; H, 6.95; N, 6.66.

Found: C, 74.28; H, 7.02; N, 6.58.

Data of X-ray powder diffraction analysis

Diffraction angle: 2θ(°)	Spacing: d value (angstrom)
5.08	17.4
10.2	8.68
16.8	5.27
17.8	4.97
18.6	4.76
20.6	4.31
23.1	3.85

Formulation Example 4

(1) Crystals in Example 1	1 g
(2) Lactose	197 g
(3) Corn starch	50 g
(4) Magnesium stearate	2 g

The above-described (1), (2), and corn starch (20 g) were compounded and granulated together with a paste prepared from corn starch (15 g) and 25 ml of water. To the granules were added corn starch (15 g) and the above-described (4) and the resulting mixture was pressed by the use of a compressed tablet making machine to produce 2,000 tablets of 3 mm in diameter, each of which contains 0.5 mg of the crystals obtained in Example 1.

Formulation Example 5

(1) Crystals obtained in Example 1	2 g
(2) Lactose	197 g
(3) Corn starch	50 g

According to a procedure similar to that used in Formulation Example 4, there were prepared 2,000 tablets of 3 mm in diameter, each of which contains 1.0 mg of the crystals obtained in Example 1.

Formulation Example 6

(1) Crystals in Example 1	5.0 mg
(2) Lactose	60.0 mg
(3) Corn starch	35.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

By the use of 0.03 ml of a 10% aqueous solution of gelatin (containing 3.0 mg of gelatin), a mixture of the above-described substances (1), (2), and (3) was granulated by passing through a sieve with a 1-mm mesh and the resulting granules were dried at 40°C and then sieved again. The thus-obtained granules were mixed with the above-described (5) and pressed. The thus-obtained core tablets were sugar-coated by treatment with a suspension of sucrose, titanium dioxide, talc, and gum arabic in water. The resulting sugar-coated tablets were glazed with wax to obtain the coated tablets.

Experimental Example 5

Determination of the activity to inhibit the acetylcholine esterase

The activity to inhibit the acetylcholine esterase of the crystals obtained in Example 1 was determined according to the acetylthiocholine method (the Ellman method) by the use of a human erythrocyte-derived acetylcholine esterase.

A human erythrocyte-derived acetylcholine esterase (Sigma Chemical Company) was dissolved into distilled water to obtain a standard enzyme preparation with an enzyme concentration of 0.2 IU/mL. To a 96-well titer plate were dispensed 20 µl of the drug-containing solution, 30 µl of an 80-mM solution of Tris-HCl (pH 7.4), 50 µl of the standard enzyme preparation, and 50 µl of a 5-mM solution of 5,5-dithio-bis(2-nitrobenzoic acid) (Sigma Chemical Company) and the microplate was shaken for 10 seconds. As soon as 50 µl of a 4-mM solution of acetylthiocholine iodide (Sigma Chemical Company) was added and shaking was started again, every increment in

absorbance at the wavelength of 414 nm at an interval of 30 seconds was determined for 10 minutes.

$$R = 5.74 \times 10^{-7} \times \Delta_A$$

(wherein R indicates an enzyme activity (mol) and Δ_A indicates an increment in absorbance at the wavelength of 414 nM). The experiment was repeated at least three times with each compound to determine the 50% inhibitory concentration (IC_{50}). Furthermore, the activity to inhibit the acetylcholinesterase of distigmine was determined in a manner similar to that described in the above method. The results obtained are shown in the following Table.

Compounds	IC_{50} (nM)
Example 1	6.6
Distigmine	651.9

The results described above reveal that the crystals of the present invention possess an excellent activity to inhibit the acetylcholinesterase.

Experimental Example 6

Hygroscopicity test

In weighing vessels, 0.3 g of the crystals, which were obtained in Example 1, was weighed and the vessels were stored for the period of 14 days in the desiccators of the relative humidity (RH) of 75% (a saturated aqueous solution of sodium chloride) and of 93% (a saturated aqueous solution of potassium nitrate), with the vessels being opened. After this period, the percent changes in the weight were determined. The results obtained are shown in the following table.

Period of storage (days)	Percent change in weight (%)	
	25°C/75% RH	25°C/93% RH
4	+ 0.11	+ 0.06
7	+ 0.11	+ 0.09
14	+ 0.18	+ 0.15

The results described above reveal that no changes were observed in the weight of the crystals of the present invention, thereby proving a nonhygroscopic property of the crystals.

In addition, the X-ray powder diffraction images of the crystals remained

they are useful as prophylactic or therapeutic agents for dysuria, particularly for difficulty of urination.

Conclusion

The crystals of the present invention possess an excellent action to inhibit acetylcholinesterase and an action to improve the excretory potency of urinary bladder and are low in the toxicity, thereby being useful as drugs. Also, the crystals of the present invention are high in their purity, high in their quality, low in their hygroscopic property, and extremely excellent in their stability without being deteriorated upon a long-term storage under the usual conditions.

The entire specification and claims of parent U.S. application S.N. 09/787,288 and JP 2001-85190 are incorporated by reference herein.

ABSTRACT

Agents for improving potentcy of the urinary bladder which comprises an amine compound of non-carbamate-type having an acetylcholinesterase-inhibiting action. Particularly, crystals of a tricyclic, condensed, heterocyclic derivative are provided, which possess an excellent action to inhibit acetylcholine esterase and an action to improve the excretory potency of urinary bladder. As an example, crystals of of 8-[3-[1-[(3-fluorophenyl)-methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro- 4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof and pharmaceutical compositions containing them are disclosed.